*Allergology International* (2004) **53**: 211–217

Review Article

# Additive effect of cysteinyl leukotriene or thromboxane modifiers to inhaled corticosteroids in asthmatic patients

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## Abstract

Bronchial asthma is a chronic inflammatory disease of the conducting airways. Current asthma treatment guidelines recommend inhaled corticosteroids (ICS) as the first-line maintenance therapy for mild to severe persistent asthma, because ICS are the most efficacious anti-inflammatory medication. Despite treatment with ICS, suppression of inflammation is often incomplete and blockade by ICS of cysteinyl leukotriene (CysLT) and thromboxane (TX) $A_2$ biosynthesis is limited. The addition of a $CysLT_1$ receptor antagonist to an ICS represents a reasonable alternative therapeutic approach for the treatment of asthma patients whose symptoms remain uncontrolled on ICS alone. Indeed, $CysLT_1$ receptor antagonists are demonstrated both to have an additive effect to ICS therapy and to allow the reduction of ICS dosage. Thromboxane modifiers also have an additive effect with low- to moderate-dose ICS. Although the long-term usefulness of add-on therapy of CysLT or TX modifiers (*vs* long-acting $\beta_2$-adrenergic receptor agonists) to ICS is unclear, these alternatives are worthy of further consideration.

**Key words:** asthma, corticosteroid, cysteinyl leukotriene, thromboxane.

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Received 24 December 2003.

## Introduction

Bronchial asthma is a chronic inflammatory disease of the conducting airways that is characterized by bronchial hyperresponsiveness and a variable degree of bronchoconstriction. Current asthma treatment guidelines recommend inhaled corticosteroids (ICS) as the first-line maintenance therapy for mild to severe persistent asthma, because ICS are the most effective anti-inflammatory medications.[1,2] Inhaled long-acting $\beta_2$-adrenergic receptor agonists (LABA) are recommended as the first-choice add-on therapy to ICS. Adding a cysteinyl leukotriene (CysLT) modifier is a second-line option. The CysLT are important pro-inflammatory mediators, which are involved in airway smooth muscle contraction, inflammatory cell accumulation, vascular leakage and mucus hypersecretion in the asthmatic airway.

Several clinical trials have compared the clinical efficacy and safety of ICS and CysLT modifiers for the treatment of persistent asthma; these investigations have demonstrated that low-dose ICS is clinically more effective as first-line maintenance therapy for patients with persistent asthma, who are undertreated and remain symptomatic while taking a short-acting $\beta_2$-adrenergic receptor agonist alone.[3,4] However, even high doses of ICS cannot always control completely patients with moderate or severe asthma.[5] Indeed, it has been reported that combinations of anti-asthmatic drugs with different pharmacological mechanisms of action confer significant additive efficacy to therapy with ICS.[6,7]

Although antileukotriene drugs are used worldwide, the usefulness of these drugs in the treatment of asthma remains to be defined more precisely.[8,9] Furthermore, both a thromboxane (TX) $A_2$ synthase inhibitor and $TXA_2$

receptor antagonists are available for the treatment of asthma in Japan. In the present review, we address the efficacy of CysLT or $TXA_2$ inhibition in asthmatic patients receiving ICS therapy.

## Effect of corticosteroid on eicosanoid production in the lung

Although corticosteroids are potent anti-inflammatory agents, their mechanism of action remains uncertain. Some *in vitro* experiments have suggested that corticosteroids cause decreased arachidonic acid synthesis in inflammatory cells, such as alveolar macrophages pretreated with steroid.[10–12] However, *in vivo* data do not consistently demonstrate the inhibition of arachidonate synthesis with corticosteroid therapy.[13–16]

Pavord *et al*.[13] measured CysLT concentrations of induced sputum in healthy control subjects and asthmatic patients. Sputum leukotriene (LT) $C_4/D_4/E_4$ concentrations of CysLT were significantly greater in asthmatic patients taking either β-adrenergic agonists alone or in mild persistent asthmatics who were taking daily ICS (mean daily dose of beclomethasone (BDP) or equivalent = 1440 μg). A similar increase in CysLT concentrations was also observed within 48 h in subjects having an acute, severe exacerbation of asthma (Fig. 1). These results suggest that CysLT produced in asthmatic airways are not inhibited by high-dose ICS. O'Shaughnessy *et al*.[14] demonstrated that inhaled fluticasone propionate (1000 μg/day) administered over a 2 week period inhibited both the early and late bronchoconstrictor response to inhaled allergen, but did not prevent allergen-evoked urinary $LTE_4$ excretion. This also indicates that administration of high-dose ICS does not block antigen-induced CysLT production in the airway.

In another investigation, the effect of oral prednisone for 6–9 days on eicosanoid concentrations in bronchoalveolar lavage (BAL) fluid was determined in 14 atopic asthmatic volunteers at baseline and after allergen instillation.[15] Prednisone reduced symptoms and inhaler use, but had no significant effect on eicosanoid concentrations in BAL fluid. Prednisone did not decrease the concentration of urinary $LTE_4$ at baseline or after allergen challenge.

In addition to CysLT, airway TX synthesis is also increased in the airways of severe asthmatic patients.[16] This increase in TX concentrations in BAL fluid persists in severe asthmatic patients taking large doses of oral corticosteroids (> 35 mg/day prednisone), suggesting that it is also unlikely that corticosteroids inhibit TX production in the asthmatic airway.

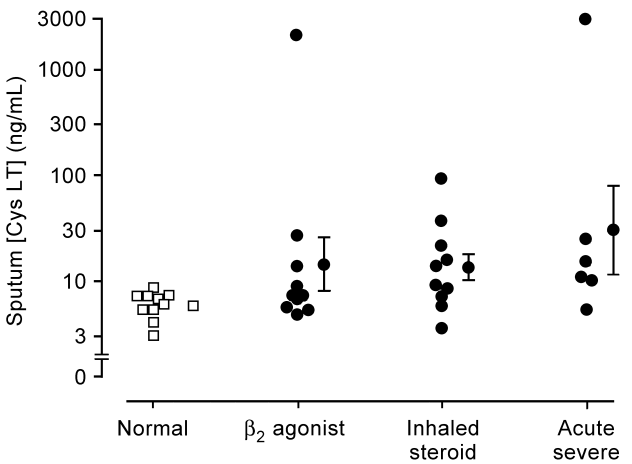


**Fig. 1** Sputum cysteinyl leukotriene (CysLT) concentration in healthy and asthmatic subjects. Subjects with asthma were subdivided into those with mild episodic asthma requiring treatment with an inhaled $\beta_2$-adrenergic receptor agonist (as needed) only ($n$ = 10) and those with persistent asthma requiring regular treatment with inhaled corticosteroids ($n$ = 10). Six subjects receiving 30 mg prenisolone daily were studied within 48 h of an exacerbation of asthma. Sputum leukotriene $C_4/D_4/E_4$ concentrations were significantly greater in subjects with asthma than in normal controls. Reproduced with permission from Pavrod *et al*.[13]

Louis *et al*.[17] demonstrated that significant, residual eosinophilic inflammation (as marked by increased eosinophil cationic protein) persisted in patients with moderate and severe asthma after treatment with either high doses of ICS or oral corticosteroids. Thus, treatment with high-dose oral corticosteroids does not fully resolve eosinophilic inflammation in patients with persistent asthma.[17] Accordingly, current data suggest that corticosteroids have no significant inhibitory effect on eicosanoid production in the airway and do not modulate asthmatic inflammation caused by CysLT or TX.

## Additive effects of CysLT antagonists on ICS therapy

Although current guidelines recommend ICS as first-line treatment for patients with persistent asthma,[18] many patients remain symptomatic despite ICS treatment. Increasing the dose of ICS is one therapeutic option. However, several lines of evidence also suggest the possibilities of alternative strategies. Laviolette *et al*.[19] examined the additive effect of montelukast, a $CysLT_1$

receptor antagonist, to low-dose ICS therapy in asthmatics, who were not controlled adequately with corticosteroid doses equivalent to 400–500 μg BDP. They demonstrated that montelukast provided additional control of asthma and, although montelukast had only approximately one-half of the bronchodilatory effect of 400 μg BDP, the combination of these two medications resulted in augmented improvement in forced expiratory volume in 1 s ($FEV_1$; Fig. 2). The addition of the $CysLT_1$ receptor antagonist zafirlukast to ≥ 1200 μg/day equivalent dose of BDP further improved pulmonary function and asthma symptoms and reduced the risk of asthma exacerbations.[20] These data suggest that asthma symptoms and exacerbations caused by CysLT may not always be controlled adequately by high-dose ICS alone.

Price *et al*. compared the clinical benefits of adding montelukast to budesonide against doubling the budesonide dose for 12 weeks in adults with asthma inadequately controlled by inhaled budesonide (800 μg/day).[21] A faster onset of action was observed in the montelukast group and both groups showed comparable improvement over the 12 week therapeutic period. This report suggests that the addition of montelukast to inhaled budesonide can be an effective and well-tolerated alternative to doubling the dose of inhaled budesonide in adult asthma patients experiencing symptoms and inadequate control on budesonide alone.

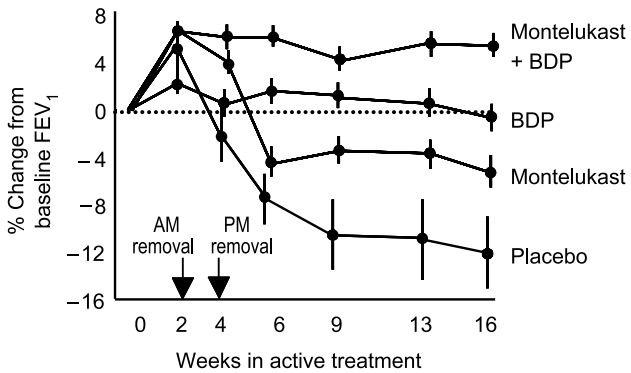


**Fig. 2** Effect of the addition of montelukast or inhaled corticosteroids on forced expiratory volume in 1 s ($FEV^1$; mean ± SEM) as a percentage change from baseline. Treatment groups are as follows: (i) montelukast 10 mg + beclomethasone (BDP) 400 μg (montelukast + BDP group); (ii) placebo + BDP 400 μg (BDP group); (iii) montelukast + inhaled placebo (montelukast group); and (iv) placebo + inhaled placebo (placebo group). AM and PM removal, morning and evening BDP inhaler, respectively, were replaced with a placebo inhaler in the placebo and montelukast groups. The withdrawal of BDP caused a decrease in $FEV_1$, which was attenuated by approximately half, in the montelukast group compared with the placebo group. The addition of montelukast to BDP caused an increase in $FEV_1$, which exceeded the effect of BDP alone. Reproduced with permission from Lavoilette *et al*.[19]

The $CysLT_1$ antagonists may also allow for a reduction in dosage of ICS and/or oral corticosteroids. Patients with severe asthma require daily medication with anti-inflammatory agents, most commonly oral and high-dose ICS. Although ICS are effective in the long-term treatment of asthma, there are significant concerns for the long-term use of these drugs, including impairment of growth and development in children, the development of osteoporosis and the suppression of the hypothalamic–pituitary–adrenal axis.[22–25] Prior studies have shown that adding a $CysLT_1$ receptor antagonist to ICS in patients with uncontrolled asthma improves asthma control.[19–21] The ICS-reducing capability of a $CysLT_1$ receptor antagonist has been demonstrated in several independent investigations.[26–28] Tohda and Fujimura *et al*.[26] demonstrated that montelukast reduced the need for ICS while maintaining asthma control over a 24 week period. After a 4 week run-in period, 191 moderate-to-severe asthmatic patients whose asthma had been well controlled with daily ICS therapy (BDP 800–1600 μg/day) were randomly assigned to one of two treatment groups (placebo or montelukast) in a 24 week, multicentre, double-blind study. After a 50% reduction in the ICS dose every 8 weeks, morning and evening peak expiratory flow rates (PEFR) were maintained over the 24 week treatment period in the montelukast group. These data suggest that $CysLT_1$ receptor antagonists may be useful for sustained treatment in patients with asthma who require high doses of ICS and that the dose of ICS may be decreased for significant periods in these patients.[26]

Although the mechanism of the additive effect of leukotriene modifiers with ICS is unclear, it has been reported that airway responsiveness to AMP and surrogate indices of inflammation, such as exhaled nitric oxide and blood eosinophils, are attenuated by the addition of montelukast.[29]

## Long-acting $\beta_2$-adrenergic receptor agonists versus CysLT

The addition of a LABA or $CysLT_1$ receptor antagonist to ICS has been recommended in asthmatic patients whose symptoms remain uncontrolled on ICS.[1,2] Prior studies have shown that the addition of either a LABA or an

antileukotriene is more effective at controlling asthma symptoms than increasing the dose of corticosteroid alone.[30,31] Recently, a randomized, controlled trial has been reported in which the efficacy of adding montelukast versus ICS to salmeterol was compared.[32] The percentage of patients with asthma exacerbations was used as the primary end-point and the results were comparable in both groups. Asthma exacerbations occurred in only 20.1% of patients receiving montelukast + fluticasone and 19.1% of patients treated with salmeterol + fluticasone. Although salmeterol + fluticasone caused a greater increase in $FEV_1$ and morning PEFR than montelukast + fluticasone, asthma-specific quality of life and nocturnal awakenings were similar between the groups. The conclusion of this study was that the addition of montelukast in patients whose symptoms remained uncontrolled by inhaled fluticasone could provide equivalent clinical control to salmeterol. However, the current guidelines do not recommend this alternative as the first-line therapy for moderate or severe (level III or IV) asthmatics.[1,2]

Bronchodilatory effects have been used as a primary end-point in clinical trials for examining the efficacy of anti-asthmatic drugs. The LABA are bronchodilators and do not have an anti-inflammatory effect, whereas CysLT antagonists block CysLT-induced airway reactions, such as bronchoconstriction, airway leakage and airway eosinophilia Nonetheless, the bronchodilatory effect of LABA in patients with asthma, as assessed as $FEV_1$ and PEFR, exceeds that of leukotriene modifiers.

## Additive effects of CysLT antagonists to ICS in patients with aspirin-induced asthma

Asthma attacks caused by aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) are the hallmark of aspirin-induced asthma (AIA), which has been observed in approximately 5–15% of adult asthmatic patients.[33] Both exhaled CysLT and urinary excretion of $LTE_4$ are increased by two- to 10-fold in patients with AIA compared with patients with aspirin-tolerant asthma (ATA); this corresponds to clinical evidence of constitutive, genetic overexpression of the $LTC_4$ synthase.[34,35] Aspirin challenge causes an increase in CysLT levels in BAL fluid and urine[34,36] and antileukotrienes prevent aspirin-induced bronchoconstriction.[37] These findings suggest that CysLT has a critical role in AIA. Furthermore, antileukotrienes may be more effective in patients with AIA compared with ATA. Dahlen *et al*. evaluated the benefits of adding the $CysLT_1$ receptor antagonist montelukast to a group of patients with AIA and moderate to severe asthma receiving conventional controller therapy, including corticosteroids.[38] The addition of montelukast improved pulmonary function and the control of asthma beyond that which was achieved by conventional anti-asthmatic controller therapy. There was a striking 54% decrease in the incidence of asthma exacerbations. The baseline treatment included inhaled, inhaled and oral or only oral corticosteroids in 90% of patients receiving montelukast. Interestingly, the therapeutic response to montelukast included patients with different baseline characteristics and did not correlate with baseline urinary $LTE_4$. Accordingly, the mechanism for the superior efficacy of antileukotriene therapies in AIA remains undefined.

## Additive effects of $TXA_2$ antagonists on ICS therapy

It has been reported that the inhaled TX mimetic U46619 is a potent bronchoconstrictor in normal and asthmatic subjects and that sub-threshold concentrations

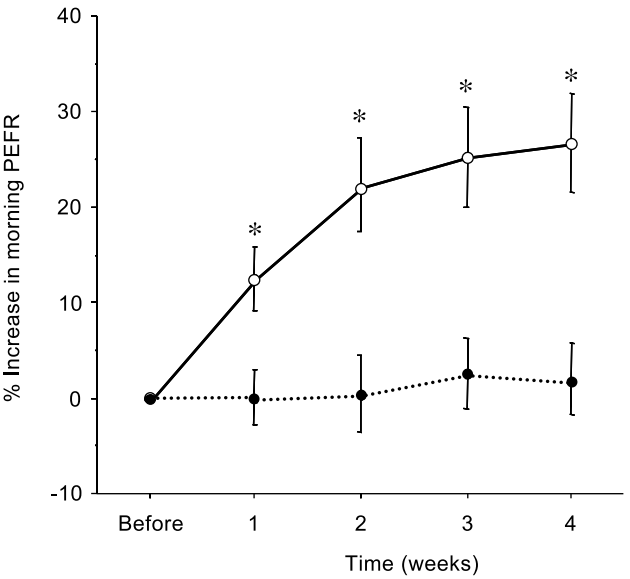


**Fig. 3** Mean (± SEM) values for the percentage increases in morning peak expiratory flow rate (PEFR) caused by treatment with the thromboxane synthesis inhibitor ozagrel hydrochloride (○) or placebo (●) in asthmatic patients undergoing beclomethasone inhalation therapy (800 μg/day) for 8 weeks or more. *$P < 0.01$. Reproduced with permission from Fujimura *et al*.[45]

of U46619 cause airway hyperresponsiveness to methacholine in asthmatic subjects.[39] Thromboxane synthetase inhibitors suppress bronchoconstriction caused by various bronchoconstrictive agents[40] and $TXA_2$ has been implicated in acute bronchoconstriction after allergen inhalation in asthmatics.[41,42] We have also reported that the selective TX synthetase inhibitor ozagrel hydrochloride[43] or the TX receptor antagonist seratrodast[44] reduce bronchial hyperresponsiveness in asthmatic patients. Accordingly, $TXA_2$ may be a significant mediator in the pathophysiology of asthma. Both $TXA_2$ synthase inhibitors and $TXA_2$ receptor antagonists are available for the treatment of asthma in Japan.

Fujimura *et al*. examined the efficacy of the add-on use of ozagrel hydrochloride, a TX synthetase inhibitor, to ICS in 70 asthmatic patients uncontrolled on 800 μg/day BDP (Fig. 3).[45] Ozagrel hydrochloride had an additive effect to ICS compared with placebo. An increase in PEF was observed in approximately 30% of patients receiving ozagrel hydrochloride. Fukuoka *et al*. have shown that seratrodast, a $TXA_2$ receptor antagonist, improves PEFR and bronchial hyperresponsiveness in asthmatic patients uncontrolled on 400 μg/day BDP.[46] Seratrodast also reduced the concentration of eosinophil cationic protein in sputum.[46] These reports indicate that TX inhibition improves clinical symptoms and airway hyperresponsiveness by reducing airway inflammation when added to low to moderate doses of ICS. There is evidence suggesting that the ratio of urinary eicosanoids may predict of the efficacy of $TXA_2$ receptor antagonism.[47] Where the ratio of urinary 11-dehydro-$TXB_2$/$LTE_4$ was high (18 of 45 subjects; 40%), there was a corresponding decrease in the asthma symptom score after treatment with seratrodast.

The additive efficacy of ICS and TX inhibition on eosinophilic inflammation in asthmatic airways remains to be fully elucidated. In one prior report, treatment with seratrodast reduced: (i) the number of submucosal $EG2^+$ eosinophils; and (ii) the numbers of cells expressing monocyte chemotactic protein-3, RANTES, macrophage inflammatory protein-1α and eotaxin in the submucosa of asthmatic airways.[48]

We conclude that although corticosteroids (ICS or oral) are the most efficacious anti-inflammatory agents for the treatment of asthma, corticosteroids do not block inflammatory responses elicited by CysLT or TX. Recent investigations suggest that adding a CysLT or TX modifier may be a useful therapeutic alternative for patients not responding adequately to ICS.

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